Impact of glycemic control over cardiac autonomic neuropathy

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Received: 13 August 2020 / Revised: 13 August 2020 / Accepted: 5 October 2020 / Published online: 8 October 2020
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Abstract

Purpose Cardiovascular autonomic neuropathy (CAN) is one of the most common and serious complications associated with diabetes and is defined as the impairment of the autonomic control of the cardiovascular system, whose prevalence in Indian population has been reported to be > 50%. The risk factors associated with CAN include hyperglycemia, duration of diabetes, hypertension, dyslipidemia, and obesity. This study was conducted to examine the association of CAN with its determinants among diabetics.

Methods Socio-demographic characteristics were noted along with performance of biochemical analyses of blood samples according to standard hospital pathology laboratory protocols. Clinical assessment of CAN comprised a of 5 indexes, including 3 heart rate variability parameters (resting tachycardia, Qtc interval > 440 msec, exercise intolerance) and 2 blood pressure parameters (orthostatic hypotension, abnormal hand gripping test).

Results The odds of CAN increased with poor glycemic control (FBS $\geq$ 126 mg/dL (OR = 1.17 (1.02–10.68); 2 hr PPBS $\geq$ 200 mg/dL (OR 1.63 (1.26–8.82) and HbA1c $\geq$ 6.5% (OR = 10.68 (1.54–208.02). Significant difference was also found in relation to duration of diabetes, weight and body mass index of the participants with various grades of CAN.

Conclusions CAN is associated strongly with poor glycemic control. Obesity seems to be involved in the impairments of the cardiac autonomic function and this factor must therefore be taken into account in future studies when interpreting the results. Body mass control and glycemic control could provide an important approach to reducing CAN.

Keywords Diabetes · Diabetic Autonomic Neuropathy · Diabetic Complications · Cardiovascular Diseases

Introduction

Diabetes Mellitus (DM) is a problem of major concern and has been characterized as the primary health care challenge of the twenty-first century. It is a global epidemic affecting about 8.3% of the global population with a significant proportion (50%) remaining undiagnosed [1]. Currently, type 2 diabetes mellitus (T2DM) is an epidemic development throughout the world. Data from the International Diabetes Federation (IDF) show that in 2015 almost 5 million patients across the world

died due to diabetes and its complications. It is estimated that almost one in six people are currently at risk of developing diabetes-related complications [2, 3].

Cardiovascular disease (CVD) is one of the leading cause of mortality and morbidity in patients with diabetes and subsequently the primary goal of treatment is to reduce the burden of CVD as well as the vascular complications associated with diabetes [3, 4]. Much of the CVD prevention strategies are based on lowering blood pressure (BP) and low density lipoprotein (LDL)-cholesterol levels and improving glycemic control [5–8]. Despite that, CVD remains very common and a major cause of mortality and morbidity in patients with DM. Hence, better understanding of pathogenesis of CVD is crucial to develop new therapeutic targets.

Cardiac autonomic neuropathy (CAN) is a common and overlooked diabetes-related complication that has a major impact on CVD. It damages autonomic nerve fibers that innervate the heart and blood vessels, in turn causing abnormalities in heart rate (HR) and vascular dynamics. It is known to affect multiple organ systems and is a major cause of morbidity and mortality in patients with diabetes [9–12]. Some studies in

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India have reported a prevalence of CAN to be as high as 53% [13].

The CAN Subcommittee of Toronto Consensus Panel on Diabetic Neuropathy defines CAN as an “impairment of cardiovascular autonomic control in patients with established diabetes after excluding other causes” [11, 14]. Risk factors associated with CAN include hyperglycemia, duration of diabetes, hypertension, dyslipidemia, and obesity [15]. Cardiovascular autonomic reflex tests are the most commonly used methods for the diagnosis of CAN and can easily assess cardiovascular autonomic function based on HR response to deep breathing, valsalva maneuver, and postural change [12, 14]. Underdiagnosed, CAN significantly exhibits multiple clinical manifestations, such as resting tachycardia, orthostasis, silent myocardial infarction, exercise intolerance, and intraoperative cardiovascular liability. These severely debilitating complications often decreases survival in patients with diabetes [11, 16].

The present study has been conducted with an objective to estimate the magnitude of association of uncontrolled blood sugar levels with CAN in a tertiary care institute of Eastern India.

Materials & methods

Study population

This cross-sectional study was conducted in (name blinded) among patients with T2DM. Inclusion criteria were as follows: apparently healthy and asymptomatic, age 30 years and older, and duration of T2DM ≥ 5 years. Patients with previous history of shock, heart failure, ischemic heart disease, hyperthyroidism, chronic renal failure, multiple system atrophy and Addison’s disease and an abnormal electrocardiogram were excluded, alongwith those on medications such as vasodilators, diuretics, antiarrhythmic, beta-blockers, alpha-agonist or alpha blocker. All patients provided written informed consent, and the study was approved by institute research ethics committees. Socio-demographic characteristics were noted alongwith performance of biochemical analyses of blood samples according to standard hospital pathology laboratory protocols.

Cardiovascular autonomic function testing

Clinical assessment of CAN comprised a battery of 5 indexes, including 3 HR variability parameters and 2 BP tests [17, 18]. Examination of HR variability was performed according to a standard protocol after a light meal. Resting electrocardiogram was performed using a standard commercial ECG machine. QTc interval ≥ 440 ms was considered as abnormal. Patients underwent maximal treadmill exercise testing according to the

Bruce protocol with simultaneous measurement of HR and BP. The HR response to exercise (chronotropic index) was calculated by HR reserve (peak HR – resting HR) as a percentage of age-predicted HR reserve [19]. BP was recorded in the right arm supine position using a sphygmomanometer. The BP was again measured after asking the patient to stand. Also, a hand gripping test was performed where the BP was measured in supine position followed by squeezing a small ball in hand for about 5 minutes while lying in bed and repeat measurement of BP. Abnormal results within the 5-test battery were defined by age- and sex-based normal values for HR variability and BP, with the total number of abnormal results defining the CAN score [17, 18].

- 1 Normal: all five tests normal or one borderline.
- 2 Mild: one of the three HR tests abnormal or two borderline.
- 3 Moderate: two or more of HR tests abnormal.
- 4 Severe: two or more of the HR tests abnormal plus one or both BP tests abnormal or both borderline.

Statistical analysis

Data were analyzed using SPSS version 21.0 (SPSS, Inc., Chicago, Illinois) and expressed as mean $\pm$ SD or median (inter-quartile range) where appropriate, after Kolmogorov-Smirnov assessment of normality of distribution. Categorical and normally distributed continuous variables were compared using the chi-square 2test and independent t-test, respectively. Skewed and ordinal variables were compared by the Mann-Whitney U test. Analysis of covariance was used to adjust for relevant group differences at baseline. Multiple logistic regression analysis was performed to isolate the role of various socio-demographic characteristics and biochemical parameters from other factors that may influence CAN (factors were retained if p-value was < 0.20). Statistical significance was defined by $p < 0.05$.

Results

General characteristics of participants

Baseline characteristics of the studied participants are shown in Table 1. At the time of the study, no significant difference was found in relation to age of the participants with various grades of CAN, but lower socio-economic status (SES) group seemed to have severe CAN as compared to those belonging to upper SES. Almost all the participants were married; with 40% having education till high school, however, no association of CAN with these socio-demographic characteristics could be established.

Table 1 Comparison of socio-demographic characteristics of participants based on severity of cardiac autonomic neuropathy

Socio-demographic Characteristics		Total (n = 88)	Normal (n = 15)	Mild (n = 22)	Moderate (n = 33)	Severe (n = 18)	p-value
Age (yr)		55.44 ± 8.28	54.53 ± 7.56	55.00 ± 9.24	57.54 ± 8.33	52.88 ± 7.17	0.25
Duration of Diabetes (yr)		7.98 ± 2.56	6.20 ± 1.78	7.27 ± 2.07	8.57 ± 2.83	9.27 ± 2.16	< 0.05*
Sex (%)	Male	59 (67.04)	9 (60.00)	15 (68.18)	22 (66.67)	13 (72.22)	0.903
	Female	29 (32.95)	6 (40.00)	7 (31.81)	11 (33.33)	5 (27.78)	
SES (%)	Low	18 (20.45)	2 (13.33)	2 (9.09)	6 (18.18)	8 (44.44)	< 0.01*
	Average	61 (69.31)	9 (60.00)	16 (72.72)	26 (78.78)	10 (55.56)	
	High	9 (10.22)	4 (26.67)	4 (18.18)	1 (3.03)	0 (0.00)	
Religion (%)	Hindu	82 (93.18)	15 (100.00)	20 (90.90)	30 (90.91)	17 (94.44)	0.66 ^a
	Muslim	6 (6.81)	0 (0.00)	2 (9.09)	3 (9.09)	1 (5.55)	
Marital Status (%)	Married	87 (98.86)	15 (100.00)	22 (100.00)	33 (100.00)	17 (94.44)	0.26 ^a
	Unmarried	1 (1.13)	0 (0.00)	0 (0.00)	0 (0.00)	1 (5.55)	
Education (%)	Till High School	35 (39.77)	5 (33.33)	7 (31.81)	11 (33.33)	12 (66.67)	0.19
	Till Intermediate	32 (36.36)	5 (33.33)	7 (31.81)	14 (42.42)	6 (33.33)	
	Graduate	21 (23.86)	5 (33.33)	8 (36.36)	8 (24.24)	0 (0.00)	

ANOVA test was used as the test of significance for continuous variables, and Chi-Square test, Fischer – Exact Test was used for the categorical variables
SES – Socio-Economic Status

* $p < 0.05$

^a Fischer Exact Test

Anthropometry parameters of participants

The mean weight of the participants was found to be 76.47kgs with those suffering from severe CAN record a higher weight (80.55 kg) as compared to those not diagnosed with neuropathy. Similar was the case with body mass index (BMI) (29.79 ± 2.85 vs. 27.40 ± 2.32 ; $p = 0.01$). However, no such association was observed with regards to height (Table 2).

Comparing the biochemical parameters of participants

Table 3 compares the biochemical parameters of participants with grades of CAN.

The patients having severe CAN also had poorer glycemic control as indexed by an increased fasting blood sugar (FBS), 2 hour post-prandial blood sugar (PPBS), random blood sugar (RBS) and glycated hemoglobin (HbA1c). Of 73 participants

with CAN, 91.78% had a FBS ≥ 126 mg/dL and 98.63% had HbA1c $\geq 6.5\%$.

Logistic regression analysis

Multivariate logistic regression analysis (Table 4) was performed to identify determinants of CAN in participants. All factors having an association ($p < 0.20$) – SES, education, duration of diabetes, weight and BMI – were considered as covariates. The odds (OR (95% confidence intervals)) of CAN increased with uncontrolled diabetes mellitus with increased biochemical parameters (FBS ≥ 126 mg/dL; 2 hr PPBS ≥ 200 mg/dL and HbA1c $\geq 6.5\%$).

Discussion

In this study, symptoms suggesting CAN were present in 73 (82.95%) of these patients. This prevalence was much higher

Table 2 Comparison of anthropometric parameters of participants based on severity of cardiac autonomic neuropathy

Parameters	Total (n = 88)	Normal (n = 15)	Mild (n = 22)	Moderate (n = 33)	Severe (n = 18)	p-value
Weight (kg)	76.47 ± 6.85	73.53 ± 5.01	73.68 ± 6.86	77.45 ± 6.38	80.55 ± 6.89	< 0.05*
Height (cm)	1.62 ± 0.06	1.64 ± 0.05	1.62 ± 0.06	1.62 ± 0.06	1.64 ± 0.06	0.50
BMI (kg/m ²)	28.84 ± 2.73	27.40 ± 2.32	28.06 ± 2.58	29.50 ± 2.62	29.79 ± 2.85	0.01*

BMI – Body Mass Index

* $p < 0.05$

Table 3 Comparison of biochemical parameters of participants based on severity of cardiac autonomic neuropathy

Parameters	Total (n = 88)	Normal (n = 15)	Mild (n = 22)	Moderate (n = 33)	Severe (n = 18)	p-value
FBS (mg/dL)	171.99 ± 37.57	141.40 ± 28.87	141.14 ± 23.31	187.88 ± 26.01	206.06 ± 28.56	< 0.05*
2 Hr PPBS (mg/dL)	259.41 ± 59.50	207.60 ± 32.56	211.86 ± 39.67	284.45 ± 41.02	314.78 ± 48.76	< 0.05*
RBS (mg/dL)	291.24 ± 92.39	225.53 ± 61.55	216.36 ± 53.83	323.39 ± 70.62	378.56 ± 80.34	< 0.05*
HbA1c (%)	9.54 ± 2.18	7.69 ± 1.60	8.00 ± 1.19	10.14 ± 1.38	11.86 ± 2.14	< 0.05*

FBS – Fasting Blood Sugar; PPBS – Post Prandial Blood Sugar; RBS – Random Blood Sugar; HbA1C – Glycated Hemoglobin

* $p < 0.05$

than in other studies done by Aggarwal et al. (70%) [18], Valensi et al. (51%) [20] and Nijhawan et al. (60%) [21] possibly because of a longer mean duration of diabetes (8 years) in the present study. CAN was assessed by 3 standard tests of HR variations that mainly depend on parasympathetic control and 2 BP tests, which results from sympathetic neuropathy. As previously done by several investigators [14, 22], CAN was here defined on the basis of at least 1 abnormal standard test. The mild variant was found in about 17.04% of the patients. Even if only moderate or severe CAN (defined by 2 or 3 abnormal standard tests respectively) was considered, CAN appeared as the most frequent complication of diabetes.

The influence of obesity on CAN function tests has been reported in type 2 diabetic patients [23, 24]. This factor may be particularly important in recently diagnosed type 2 diabetes as suggested also by the peripheral autonomic impairment in such patients [25]. The high prevalence of CAN in our participants with obesity (71.60%) again supports this finding. Another factor which was found to be significantly associated with diabetes was socio-economic status, similar to the findings reported by Sukla et al. [13]. The reason behind this

might be associated with the level of adherence to medications owing to financial constraints.

Poor glycemic control is a major risk factor for the development and progression of CAN in DM as established in earlier studies [6, 13, 16, 26]. Also, the most important risk factor for the development of both micro and macrovascular complication in diabetes mellitus patient is uncontrolled glycemic status. Magnitude and severity of dysautonomia also increases with increase blood glucose level as mentioned by Ramachandran et al. [27]. We too demonstrated a significant association between the biochemical parameters (FBS, 2-hour PPBS and HbA1c) and the development of CAN in patients with DM. Notably, the patients with uncontrolled HbA1c had the highest risk of developing CAN. This result suggests that glycemic control is an important driver of cardiac autonomic dysfunction. Brownlee [28] demonstrated that the high blood glucose level in the past determined the risk for later diabetic complication. Due to the asymptomatic period in DM with uncontrolled hyperglycemia before the establishment of the diagnosis, further diabetic complications will occur later despite the optimal glycemic control. This phenomenon known as ‘hyperglycemic or metabolic memory’ is responsible for

Table 4 Multivariate Logistic Regression of biochemical parameters with cardiac autonomic neuropathy

Parameters		n	CAN (%) (n = 73)	OR ^a	<i>p</i> - value ^a	aOR ^b	<i>p</i> - value ^b
FBS (mg/dL)	≥ 126	76	91.78	7.44	0.04*	1.17	0.03*
	< 126	12	8.21	(1.97 – 28.10)		(1.02 – 10.68)	
2-hour PPBS (mg/dL)	≥ 200	71	86.30	5.51	< 0.05*	1.63	< 0.05*
	< 200	17	13.69	(1.63 – 18.56)		(1.26 – 8.82)	
RBS (mg/dL)	≥ 140	86	97.26	0.92	0.95	0.63	0.73
	< 140	2	2.73	(0.04 – 20.18)		(0.02 – 18.23)	
HbA1c (%)	≥ 6.5	83	98.63	26.18	< 0.05*	10.68	< 0.05*
	< 6.5	5	1.36	(2.67 – 256.30)		(1.54 – 208.02)	

FBS – Fasting Blood Sugar; PPBS – Post Prandial Blood Sugar; RBS – Random Blood Sugar; HbA1C – Glycated Hemoglobin; aOR – adjusted Odds Ratio

* $p < 0.05$

^a Bivariate logistic regression analysis

^b Multivariate logistic regression analysis adjusted for factors with $p < 0.20$

the initial damage that occurs even before diabetes has been initially diagnosed. Because we evaluated glycemic control by HbA1c levels, which reflects the average blood glucose level over the past 3 months, a possible explanation of the association with development of CAN can be a history of ‘silent’ and untreated hyperglycemia, which plays a major role in hyperglycemia-induced late complications of DM.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study on 10,251 participants demonstrated that in the patients with Type-2 DM and high cardiovascular risk, the mortality rate was increased in the group receiving intensive treatment for HbA1c reduction. Also, the study demonstrated that neuropathies (somatic and autonomic) are significant risk factors for cardiovascular disease, and this particular group of patients represent a high-risk group in which intensive glucose control should be well-balanced against the mortality risk [29, 30]. The basic approach for living with DM and having fewer complications is to start treatment immediately after onset of the disease with the purpose of achieving metabolic control as much as possible. The current trend throughout the world is to restrict the prognostic perspective of diabetes based on HbA1c value, but this is not justified by the complex mechanism implicated in vascular complications of DM.

The results deduced in the study reflects strong association and an insight regarding the importance of weight control and glycemic control, however the study is not without any limitations. The sample size is less and most of the participants are more than 50 years, which could have been one of the reasons for uncontrolled biochemical parameters. The type of DM, whether type-1 or type-2 among the participants was not analyzed separately, due to limited sample and the associations may have differed under those circumstances. Though most of the confounding factors have been adjusted for in the regression analysis, the presence of any other medical/ surgical history that can influence the findings could have been analyzed, thus affecting the generalizability of the study. However, the evaluation of all the participants involved was in a detailed manner with the history and examination being done by a single observer. Appropriate measures were taken care of to ensure the elimination of any sort of bias. The biochemical estimations were carried out with utmost care to avoid any contamination and erratic findings.

Conclusions

In this series of DM patients, the prevalence of CAN is quite high and associated strongly with poor glycemic control. Obesity seems to be involved in the impairments of the cardiac autonomic function and this factor must therefore be taken into account in future studies when interpreting the results. Body mass control and glycemic control could provide an

important approach to reducing CAN. Though, the correlation of CAN with poor glycemic control is a well-established factor, the evidence behind concentrating the treatment protocol solely on the same without taking into account other confounding factors like lifestyle modification and others needs to be evaluated further.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dr. Meghanad Meher and Dr. Jayanta Kumar Panda. The first draft of the manuscript was written by Dr. Meghanad Meher and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability Can be provided upon request.

Compliance with ethical standards

Conflict of interest Not Applicable.

Ethics approval The study was approved for conduct by the Institute Ethics Committee, SCB Medical College and Hospital, Cuttack (548/16.09.2017).

Consent to participate A written informed consent was taken from all the participants explaining the study details.

Consent for publication Not Applicable.

Code availability Not Applicable.

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